03-01-04 Image AF 1653

Atty. Docket No. MAR37 P-314

CERTIFICATE OF MAILING BY EXPRESS MAIL

I hereby certify that this paper, together with all enclosures identified herein, are being deposited with the United States Postal Service as Express Mail, using label No. EV411645728US, addressed to the Mail Stop Appeal Brief - Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450, on the date indicated below.

February 27, 2004 — Date

Deborah A. Witvoet — Deborah A. Witvoet

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Art Unit	:	1653
Examiner	:	David Lukton
Applicant	:	Lars Eric Sundstrom
Appln. No.	:	09/581,397
Filing Date	:	October 2, 2000
Confirmation No.	:	9763
For	:	NEUROPROTECTIVE AGENTS

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

TRANSMITTAL OF APPEAL BRIEF
(PATENT APPLICATION - 37 CFR §1.192)

1. Transmitted herewith, in triplicate, is the APPELLANT'S BRIEF in this application, with respect to the Notice of Appeal filed on December 1, 2003.

2. STATUS OF APPLICANTS

This application is on behalf of:

___ other than a small entity.

_X_ a small entity.

A verified statement:

___ is attached.

_X_ was already filed.

3. **FEE FOR FILING APPEAL BRIEF**

Pursuant to 37 CFR §1.17(c), the fee for filing the Appeal Brief is:

X small entity	$165.00
___ other than a small entity	$330.00

Appeal Brief fee due: $165.00

4. **EXTENSION OF TERM**

The proceedings herein are for a patent application and the provisions of 37 CFR §1.136 apply.

(complete (a) or (b), as applicable)

(a) X Applicant petitions for an extension of time under 37 CFR §1.136:

Extension (months)	Fee for other than small entity	Fee for small entity
X one month	$110.00	$55.00
___ two months	$420.00	$210.00
___ three months	$950.00	$475.00
___ four months	$1480.00	$740.00

FEE: $55.00

If an additional extension of time is required, please consider this a petition therefor.

Extension fee due with this request: $55.00

5. **TOTAL FEE DUE**

The total fee due is:

Appeal Brief fee:	$165.00
Extension fee (if any)	$ 55.00
TOTAL FEE DUE:	$220.00

6. FEE PAYMENT

_X_ Attached is a check in the sum of $220.00.

___ Charge Account No. 16 2463 the sum of $_____.

A duplicate of this transmittal is attached.

7. FEE DEFICIENCY

_X_ If any additional extension and/or fee is required, this is a request therefor and to charge Account No. 16 2463.

and/or

_X_ If any additional fee for claims is required, charge Account No. 16 2463.

Respectfully submitted,

LARS ERIC SUNDSTROM

By: Price, Heneveld, Cooper, DeWitt & Litton, LLP

February 27, 2004
Date

Gunther J. Evanina
Registration No. 35 502
695 Kenmoor, S.E.
Post Office Box 2567
Grand Rapids, Michigan 49501
(616) 949-9610

GJE/daw

Atty. Docket No. MAR36 P-314
Express Mail No. EV411645728US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Art Unit	:	1653
Examiner	:	David Lukton
Applicant	:	Lars Eric Sundstrom
Appln. No.	:	09/581,397
Filing Date	:	October 2, 2000
Confirmation No.	:	9763
For	:	NEUROPROTECTIVE AGENTS

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

APPELLANT'S BRIEF (37 CFR §1.192)

This brief is in furtherance of the Notice of Appeal, filed in this case on December 1, 2003.

The fees required under §1.17(f), and any required petition for extension of time for filing this brief and fees therefor, are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

This brief is transmitted in triplicate. (37 CFR §1.192(a)).

This brief contains these items under the following headings, and in the order set forth below (37 CFR §1.192(c)):

I. Real Party in Interest
II. Related Appeals and Interferences
III. Status of Claims
IV. Status of Amendments
V. Summary of Invention
VI. Issues
VII. Grouping of Claims
VIII. Arguments
IX. Conclusion

Appendix of Claims Involved in the Appeal

The final page of this brief bears the attorney's signature.

I. Real Party in Interest

The real party in interest in this application is University of Southampton, Highfield Southampton, Hampshire SO17 IBJ, United Kingdom, the Assignment to which was recorded at Reel 011147, Frames 0866-0868.

II. Related Appeals and Interferences

There are not any related appeals or interferences which will directly affect, or be directly affected by, or have a bearing on, the Board's Decision in this Appeal.

III. Status of Claims

This is an Appeal from the rejection of claims 1, 2, 5, 6, 8 and 19-24. The remaining claims pending in the application (3, 4, 7, and 9-18) have been withdrawn from consideration pursuant to an election of species requirement, and, therefore, should be added back into the application upon a finding that the independent claims are allowable. No claims have been allowed.

IV. Status of Amendments

Appellant has not filed an amendment after the Final Rejection. All previous amendments were entered.

V. Summary of the Invention

The invention is directed to a class of polyamine compounds in substantially pure form that provide a useful neuroprotective effect without adverse side effects. The claims are not directed to the compounds *per se*, but instead are directed to substantially pure compounds, specifically a particular class of polyamine neuroprotective agents "having less than 1%

contaminants." The difference between known impure compositions and the claimed substantially pure compounds is that the known compositions contain high levels of toxic compounds and do not have a known clinical utility. In contrast, Appellant's substantially pure compounds provide effective neuroprotection against the effects of ischaemia, such as occurs with stroke patients and patients who have suffered serious head injuries, thereby preventing brain damage. Appellant's discovery is an important advance in the art which is neither taught nor suggested. It represents the difference between useless toxic compositions that are only a laboratory curiosity, and clinically useful compositions that have the potential of preventing and/or reducing brain damage, thereby improving the quality of life and/or saving life.

VI. Issues

The issues under consideration in this Appeal are as follows:

A. Whether claims 1, 2, 5, 6, 8 and 19-24 are unpatentable under 35 U.S.C. §103 based on the teachings of United States Patent No. 5,242,947 (hereinafter referred to as "Cherksey").

B. Whether claims 1, 2, 5, 6, 8 and 19-24 are unpatentable under 35 U.S.C. §103 based on the teachings of the Cherksey patent in view of Bodansky, *Int. J. Pept. Prof. Res.* 25, 449-474, 1985 (hereinafter referred to as "Bodansky").

C. Whether claims 1, 2, 5, 6, 8 and 19-24 are unpatentable under 35 U.S.C. §103 based on the teachings of the Cherksey patent in view of the Aldrich Catalog, 1992-1993 Edition, (hereinafter referred to as "Aldrich").

D. Whether claims 1, 2, 5, 6, 8 and 19-24 are unpatentable over the Cherksey patent in view of Eldefrawi, *Proc. Natl. Acad. Sci. U.S.A.*, 85 (13), 4910-13, 1988 (hereinafter referred to as "Eldefrawi").

E. Whether claims 1, 2, 5, 6, 8 and 19-24 are unpatentable over the Cherksey patent in view of Hashimoto, *Tetrahedron Lett.*, 28 (30), 3511-14, 1987 (hereinafter referred to as "Hashimoto").

F. Whether claims 1, 2, 5, 6, 8 and 19-24 are unpatentable over the Cherksey patent in view of the Bodansky reference, and further in view of the Aldrich reference.

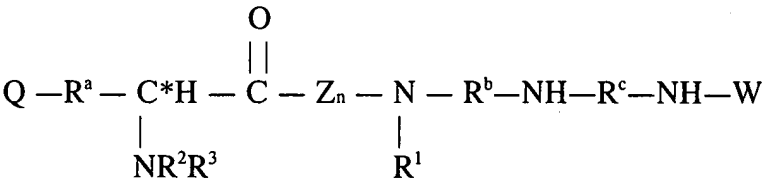
VII. Grouping of Claims

For purposes of this Appeal only, claims 1, 2 and 8 stand together; and claims 5, 6 and 19-24 stand together.

VIII. Arguments

A. Rejection Based On Cherksey

All pending claims (1, 2, 5, 6, 8 and 19-24) have been rejected under 35 U.S.C. §103 as being unpatentable over Cherksey (U.S. Patent No. 5,242,947). The Examiner has stated that the Cherksey patent teaches various compounds falling within the scope of the claimed genus. This is incorrect. The claims are not directed to the compounds disclosed by the Cherksey patent, but instead are directed to substantially pure compounds "having less than 1% contaminants," and having the formula (I)



(I)

wherein, among other things, the chiral carbon atom indicted by the asterisk is in the L-configuration. The Cherksey patent does not teach or suggest substantially pure compounds of the type claimed having less than 1% contaminants, and does not teach or suggest the required optical purity. In fact, it is clear from the evidence of record (the Declaration under Rule 1.132 of Dr. Lars E. Sundstrom signed October 24, 2001, and the Supplemental Declaration Under Rule 1.132 signed March 2, 2003) that the Cherksey patent does not provide enablement for the claimed substantially pure compounds having less than 1% contaminants, but instead discloses synthesis techniques that yield compositions which are 99% impure. As a result,

rather than providing the claimed therapeutically effective neuroprotective agents, the Cherksey patent discloses methods of preparing compounds in an impure, toxic and non-therapeutic form. Further, as indicated by the evidence of record (the Sundstrom Declarations), the Cherksey patent does not provide enablement for the substantially pure compounds.

The Cherksey reference also expressly teaches (column 20, lines 20-29) that compounds B and R are lethal to rats.

The Examiner has framed the obviousness inquiry as involving "fundamentally two issues." According to the Examiner, the first issue is whether "the disclosure of various compounds falling within the scope of the claimed genus [is] sufficient to render the claimed genus obvious." Applicant has disclosed and provided enablement for therapeutically effective neuroprotective agents in substantially pure form containing less than 1% contaminants, whereas the Cherksey patent teaches the preparation of 99% impure, toxic, non-therapeutic compositions that do not have any known utility, except as laboratory curiosities.

The second fundamental issue according to the Examiner is whether the Cherksey patent provides "an adequate description and an enabling disclosure of how to synthesize the claimed compounds." The evidence of record clearly demonstrates that Cherksey does not provide enablement for the claimed substantially pure compounds having less than 1% contaminants, and wherein the chiral atom is in the L-configuration. According to the Examiner, "while the reference may not disclose that the compounds 'must' be of the L-configuration, the reference does provide both an explicit teaching of the L-configuration and an implicit teaching of the same." The Examiner's reasoning is as follows:

> First, the convention among peptide chemists is for the stereo chemistry of a given amino acid (or molecule containing an amino acid) to be of the L-configuration unless indicated otherwise. Thus, the ordinarily skilled peptide chemist would have regarded the chiral center (of the carbon bearing the alpha-amino group) of the various compounds in columns 7-12 as being of the L-configuration since there is no indication to the contrary. In addition, the L-isomer of arginine was used rather than the D-isomer in the procedure to which applicants have referred (col 18,

> line 54+). Thus, the reference provides direction to use the L-isomer, rather than the D-isomer. Further, even if one wishes to argue that the compounds disclosed in cols 7-12 refer to a Markush group of the "D" isomer and the "L" isomer, there are at most only two possibilities, in which case both are obvious.

The Examiner's admission that "the reference does not disclose that the compounds 'must' be of the L-configuration," when compared with his statement that "the reference does provide both an explicit teaching of the L-configuration and an implicit teaching of the same," is contradictory and confusing. It appears that the Examiner is attempting to argue that the disclosure of L-arginine ethyl ester as a starting material (for Example 2 at column 18) is the same as an express teaching of the claimed substantially pure compounds. This is an argument without merit. A disclosure of a starting material having a chiral atom in the L-configuration is not a teaching or suggestion for the claimed substantially pure compounds having less than 1% contaminants wherein the chiral carbon is in the L-configuration. The evidence of record (Dr. Sundstrom's Declarations) shows that when the synthesis techniques disclosed by the Cherksey patent are used, the result is an extremely impure (at least 99% impure) highly toxic composition. Thus, the Cherksey patent does not teach or suggest the substantially pure compounds as claimed, and does not provide enablement for the substantially pure compounds as claimed.

Further, the proportion of any compound produced using the teachings of the Cherksey patent that is in the L-configuration as opposed to the D-configuration is merely speculation. As previously stated, the very high pH of 14 used in Example 2 of the Cherksey patent would lead to loss of stereochemical integrity and further impurities. Regardless, the use of L-arginine ethyl ester as a starting material is neither an explicit nor implicit disclosure of the claimed compounds, which are required to be in the L-configuration and contain less than 1% contaminants.

The Examiner's reasoning that the compounds produced in accordance with the teachings of the Cherksey patent must be in the L-configuration, "since there is no indication to the contrary," is incorrect. The same reasoning could be used to argue that the compounds

must be in the D-configuration "since there is no indication to the contrary." Neither argument is valid, and both must be dismissed.

The Examiner has argued that the claimed substantially pure compounds of formula I having less than 1% contaminants would have been obvious since "there are at most only two possibilities, in which case both are obvious." This is incorrect. A third possibility is an impure mixture of both the D-isomer and the L-isomer. Most synthetically produced compounds are mixtures comprising both the D-isomer and the L-isomer. Without motivation those having ordinary skill in the art would not have found it obvious to employ techniques for producing an optically pure composition. The Cherksey patent does not provide any suggestion that optically pure compounds, as claimed, are desired. In fact, as discussed above and as supported by the evidence of record, the techniques described in the Cherksey patent do not provide products containing even 1% (at least 99% impurities) of the compound of formula I, regardless of stereochemistry.

The Examiner has also argued that "Cherksey does not disclose racemic mixtures" and that "in the declaration (filed 1/23/03) it is stated that no coupling between arginine and spermidine occurs to begin with, so racemization in the final product cannot occur if, as asserted, the final product is never formed." Apparently, the Examiner is attempting to argue that because the Cherksey patent does not disclose racemic mixtures, it must be disclosing optically pure compounds. Obviousness is determined by comparing the claimed invention to what is disclosed by the prior art, not by what is not disclosed by the prior art. *Graham v. John Deere*, 383 U.S.1, 148 USPQ 459 (1966).

We do not understand the Examiner's statement regarding the declaration "filed 1/23/03." There were only two declarations filed, the first was signed on October 24, 2001, and the second was signed on March 2, 2003. Further, we cannot find any statement in the declarations similar to the Examiner's statement that "no coupling between arginine and spermidine occurs to begin with." Even assuming that such statements can be extrapolated from one or both declarations, we do not understand the relevance of this statement. We suspect that the Examiner is arguing that there is not any way of determining whether

racematization occurs using the synthesis techniques of the Cherksey patent, since the evidence of record shows that none of the required product is produced. If this is in fact what the Examiner is arguing, then this supports patentability, rather than obviousness. If the prior art fails to disclose a synthesis technique for producing even a very small amount of compound in accordance with formula I, then it fails to provide a teaching, suggestion or motivation for the claimed substantially pure compound.

The Examiner has also argued that because Cherksey does not "employ the term 'substantially pure' to describe the compounds," the compositions produced in accordance with the teachings of the Cherksey patent must be 100% pure. This repeats a common pattern in the Examiner's reasoning. Specifically, the Examiner has repeatedly argued that a reference must implicitly disclose what it does not explicitly disclose. We do not expect the Board of Patent Appeals and Interferences to agree.

The Examiner has also argued that the Cherksey patent discloses substantially pure compounds as claimed because the Aldrich Catalog "lists '99.9+%' benzene as the highest grade available." Appellant is not claiming benzene at any purity level.

The Examiner has expressed some opinions regarding "purity" and "substantially pure." We do not believe that these comments have any bearing on the issues. Applicant has submitted evidence showing that the Cherksey patent does not provide the claimed substantially pure compounds of formula I having less that 1% contaminants.

The Examiner has argued that while Appellant has submitted evidence demonstrating that the Cherksey patent does not provide the claimed substantially pure compounds, "Cherksey intends for nucleophilic displacement of ethanol to occur, thereby creating an amide bond." Perhaps the Examiner is suggesting that Appellant should be denied a patent on his invention because Cherksey intended but failed to provide a therapeutically useful composition. Appellant does not expect the Board of Patent Appeals and Interferences to find any merit in this argument.

The Examiner has for the first time in the Final Rejection stated that "there remain two other issues." The first issue according to the Examiner is that the reaction procedure disclosed at column 18, lines 54+ is not the only one disclosed, and that another procedure is disclosed at column 19, lines 38+. The Examiner has stated that since there "has been no assertion that the disclosed procedure (col 19, line 38+) will fail to produce the intended compounds," the claimed invention would have been obvious to those having ordinary skill in the art. The Cherksey patent does not teach or suggest that the alternative synthesis technique at column 19, line 38+ provides the claimed substantially pure compounds having less than 1% contaminants and having a chiral atom in the L-configuration. Furthermore, Dr. Sundstrom's Declaration of October 24, 2001 states (second paragraph of page 2) as follows:

> A similar pattern of damage occurred with lysine-spermidine prepared in accordance with the methodology described in WO 93/12777 (99.7 $\pm$ 0.2% damage, n = 8, $p < 0.001$ verses control for 40 microliters; and 98.3 $\pm$ 0.2%, n = 8, $p < 0.001$ verses control for 100 microliters).

The above statement refers to the preparation of lysine-spermidine in accordance with the technique described at page 31 of WO 93/12777, which is identical to the technique disclosed at column 19, line 38+ of the Cherksey patent. As will be evident from a careful review of the Cherksey patent and Appellant's Declaration of October 24, 2001, the arginine-spermidine referenced in the declarations was prepared in accordance with the disclosure at column 18, line 62+ and the lysine-spermidine was prepared in accordance with the synthesis technique described at column 19, line 38+ of the Cherksey patent. Neither technique provided a detectable amount of the desired product as determined by mass spectrophotometry, which means that the disclosed techniques produced an extremely impure composition having less than 1% of the desired product. Thus, as stated in Dr. Sundstrom's Declaration dated October 24, 2001, the Cherksey patent discloses "processes for synthesizing compounds which are neither pure nor non-toxic, and which would not anticipate or suggest the substantially pure compounds claimed in the above-referenced application."

Finally, the Examiner has argued that even if the Cherksey patent fails to disclose synthesis methods for the claimed substantially pure compounds having less than 1% contaminants, the claimed invention is obvious because "the claimed compounds *per se* are nevertheless disclosed." Appellant has provided evidence (in the form of declarations) showing that the Cherksey patent does not provide enablement for the claimed substantially pure compounds having less than 1% contaminants, but instead only discloses compositions that are at least 99% impure, extremely toxic, and without any therapeutic utility. It is well settled that the prior art must sufficiently describe the claimed invention to have placed the public in possession of it. *In Re Sasse*, 629 F2d 675, 681, 207 USPQ 107, 111, (CCPA 1980). Even if a claimed invention is disclosed in a printed publication, that disclosure does not teach or suggest the invention if it does not provide enablement for the invention. *In Re Borst*, 345 F2d 851, 855, 45 USPQ 554, 557 (CCPA 1965, *cert. denied)*, 384 US 973, 148 USPQ 771 (1966).

For the reasons above, it is respectfully submitted that the Cherksey patent does not teach or suggest the claimed invention, and does not provide motivation or enablement for the claimed invention. Therefore, the claimed invention is patentable over the teachings of the Cherksey patent.

B. Rejections Based On The Cherksey Patent In View Of The Bodansky Reference

The Examiner's first argument with respect to the Cherksey patent in view of Bodansky is that Appellant has not provided evidence that the compounds disclosed in Cherksey are not useful, but instead has only provided evidence that the products of the techniques disclosed by the Cherksey patent produce a mixture that "is cytotoxic, and therefore might not be useful." We do not understand the relevance of this argument. Perhaps the Examiner is attempting to show that compositions prepared in accordance with the teachings of the Cherksey patent may have some unknown utility, even if they do not meet the requirements of the claims or have any known

therapeutic utility. Appellant agrees that the compositions prepared in accordance with the teachings of the Cherksey patent may have some unknown utility that will be discovered. However, this is not relevant to patentability of the claims at issue.

The Examiner stated that Appellant has incorrectly alleged that the prior art does not teach the desirability of the claimed compounds, and that Cherksey discloses that the compounds are useful for regulating cationic transport and therefore discloses the desirability of the compounds. Appellant has not argued that the Cherksey patent does not teach the desirability of the compounds themselves. Instead, Appellant has argued that the Cherksey patent does not teach the desirability of the claimed invention, which is not the compounds *per se*, but is instead a "substantially pure compound having less than 1% contaminants." There is a difference between the compounds *per se*, and the claimed substantially pure compounds having less than 1% contaminants. The compositions disclosed by the Cherksey patent are at least 99% impure, extremely toxic, and without therapeutic utility. These facts are of record in the declarations of Dr. Sundstrom. In contrast, the claimed substantially pure compounds contain less than 1% contaminants and may provide excellent therapeutic results that could save lives and/or improve the quality of the lives of victims of serious head injuries and stroke patients.

The Examiner has stated that Appellant has argued that the prior art (the Cherksey patent) only discloses synthesis techniques that provide unsatisfactory results. The Examiner has also admitted that "it is probably true that no reference of record discloses that the procedure at column 18, line 54+ of Cherksey will provide unsatisfactory results." However, the Examiner has offered his opinion that "a chemist of ordinary skill, considering the teachings of Bodansky, would have recognized the need for adequate protection of the amino groups," and "that activation of the carboxyl group would have been necessary." The Examiner has relied on the following disclosure of Bodansky:

> Carboxylic acids and amines do not yield amides spontaneously. Hence, formation of the peptide bond requires activation of one of the participating components . . . the carboxyl component has to be converted to a reactive form.

Based on this disclosure, the Examiner has concluded that those of ordinary skill in the art "would have been motivated to use one of the various methods of activating carboxylic acids such as a mixed anhydride or a nitrophenyl ester, or a carbodiimide." This argument is without merit. As previously pointed out by the Examiner, one of the techniques disclosed by the Cherksey patent for preparing lysine-spermidine may be found at column 19, lines 38+ of the Cherksey patent. In this technique, an equimolar mixture of lysine and spermidine in water are reacted in the presence of an equilmolar amount of a water-soluble carbodiimide. As previously stated, this technique does not yield the claimed substantially pure compounds having less than 1% contaminants, but instead provides a composition that is at least 99% impure, extremely toxic, and without any known therapeutic utility. Thus, the use of a carbodiimide is already disclosed in the Cherksey patent, and Appellant has already provided evidence that the use of a carbodiimide does not necessarily result in the claimed invention.

The Examiner has argued that the Cherksey patent does not provide any evidence that the teachings of Bodansky have been considered. This is incorrect. The Cherksey patent discloses a synthesis technique utilizing a carbodiimide as taught by Bodansky.

The Examiner has suggested that Cherksey may not be an organic chemist of ordinary skill in the art (see the last two lines of page 10 and the first three lines of page 11 of the Office Action). Appellant does not understand the relevance of these statements, and submits that they are not germane to patentability of the claimed invention.

Finally, the Examiner has stated that "no evidence has been presented which shows that the compounds disclosed at cols 7-12 are lethal, although it may be true that a mixture of arginine ethyl ester and spermidine is cytotoxic." The purpose of this statement is not apparent. Appellant has provided data that the compositions prepared in accordance with the teachings of the Cherksey patent are extremely toxic. The ordinary meaning (from the Second College Edition, *The American Heritage Dictionary*, Houghton, Mifflin Company, Boston (1985), page. 1282) of the word toxic is "harmful, destructive, or deadly." Regardless of whether the

compositions prepared in accordance with the teachings of Cherksey are lethal or not, they are at least 99% impure, extremely toxic, and without therapeutic utility. Most importantly, the preparation of a toxic composition in accordance with the teachings of Cherksey does not provide the claimed substantially pure compounds having less than 1% contaminants, regardless of whether or not one utilizes the carbodiimides disclosed by the Bodansky reference and the Cherksey patent itself. Accordingly, the claimed substantially pure compounds having less than 1% contaminants would not have been obvious based on the combined teachings of the Cherksey patent in view of the Bodansky reference.

C. Rejection Based on the Cherksey Patent In View Of The Aldrich Reference

The Examiner has taken the position that the claimed invention would have been obvious to one having ordinary skill in the art because the Aldrich Catalog lists the price of D-arginine as $25.00 for one gram, whereas L-arginine is listed at $5.70 for 25 grams, $14.45 for 100 grams, and $48.70 for 500 grams. It is unnecessary to rely on the Aldrich Catalog for motivation to utilize L-arginine to prepare an arginine-spermidine compound in accordance with the teachings of the Cherksey patent. The Cherksey patent expressly discloses the use of L-arginine ethyl ester as a starting material at column 18, lines 54+. This disclosure is more relevant than the Aldrich Catalog, and has already been addressed above with respect to the rejection based solely on the Cherksey patent. The rejection based on the combination of the Cherksey patent in view of the Aldrich Catalog is unnecessary. Further, this combination does not address the fact that even if one utilizes L-arginine ethyl ester as a starting material (as explicitly taught by the Cherksey patent), the result is a composition that is at least 99% impure, highly toxic, and without any known therapeutic utility, and therefore does not teach or suggest the claimed invention.

D. Rejection Based On The Cherksey Patent In View Of Eldefrawi

The Examiner has stated that "there is no question as to the motivation to combine the synthetic methods of Eldefrawi with the disclosure of the target compounds given in Cherksey,"

since the Cherksey patent discloses (column 13, lines 48+) that the synthesis schemes disclosed in the Eldefrawi reference "can be employed with only such modifications, if any, as are readily apparent to those of ordinary skill in the art." More specifically, the Examiner has taken the position that the "synthetic chemist of ordinary skill would have taken from this the conclusion that in reacting a polyamine with an acylating agent (e.g., lysine or arginine+ activating agent), that all of the amino groups should be protected except for the one which is intended to form an amide bond."

The relevant portions of the Eldefrawi reference begin in the last paragraph on the right column of page 4911 and end at the bottom of the left column on page 4912. The Eldefrawi et al. reference discloses the target compounds produced at yields of about 80%. While this is much better than the techniques that are disclosed in the Cherksey patent, the combined teachings of Cherksey in view of Eldefrawi et al. would not be expected to meet the requirement of the claims for a substantially pure compound having less than 1% contaminants. Instead, the combination might be expected to provide products having a yield of about 80%, and having about 20% impurities. The modifications necessary to overcome the deficiencies in the prior art and meet the requirements of the claimed invention would not have been obvious to one having ordinary skill in the art.

E. Rejection Based On The Cherksey Patent In View Of Hashimoto

The Examiner has stated that the Hashimoto reference discloses the following reaction:

$$\text{RCO-X} + \text{spermine} \dashrightarrow \text{RCO-NH}(CH_2)_3\text{NH}(CH_2)_4\text{NH}(CH_2)_3\text{NH}_2$$

and that one having ordinary skill in the art "would have taken from Hashimoto the suggestion that reaction of an acylating agent with a symmetrical polyamine would afford the target compound."

The synthesis techniques disclosed by the Hashimoto reference provide final products (1-4) in yields of 46%, 54%, 30% and 49%, respectively. Note that these yields are after

purification using HPLC. Thus, employment of the techniques disclosed by the Hashimoto reference when applied to the synthesis of the compounds disclosed in the Cherksey patent would not be expected to yield the claimed substantially pure compounds having less than 1% contaminants. In fact, the applied prior art references demonstrate the non-obviousness of the claimed invention.

F. Rejection Based On The Cherksey Patent In View Of Bodansky And Further In View Of The Aldrich Reference

It is respectfully submitted that this rejection is unnecessary for the reasons set forth above with respect to the rejection based on the Cherksey patent in view of the Aldrich reference. The Aldrich reference adds nothing to the combination of Cherksey in view of Bodansky. The Examiner has relied on Aldrich to show that one having ordinary skill in the art would have been motivated to utilize an L-isomer as a starting material for the synthesis of compounds as taught by the Cherksey patent. However, this is unnecessary since the Cherksey patent explicitly discloses the use of L-arginine ethyl ester as a starting material in Example 2 at column 18. Although the use of an L-isomer as a starting material in a chemical reaction does not necessarily yield a product having the same chiral atom in the L-configuration, there is a more compelling argument for patentability. Dr. Sundstrom's Declaration shows that the combination of Cherksey in view of Bodansky using L-arginine ethyl ester as a starting material will provide compositions having a yield of less than 1% of the desired compound. This would not meet the requirements of the claimed substantially pure compound having less than 1% contaminants, regardless of whether the requirement for the chiral atom being in the L-configuration is met.

G. Claims 5, 6 and 19-24

Claims 5, 6 and 19-24 are patentable for all of the reasons set forth above, and separately because they include the further requirement that the composition is non-toxic. While the

Examiner has apparently questioned whether the compositions produced by the techniques of the Cherksey patent would be lethal, the Examiner has admitted that the resulting compositions may be cytotoxic. This appears to be an admission that the applied prior art references do not teach or suggest the non-toxic substantially pure compositions as claimed. Accordingly, claims 5, 6 and 19-24 are separately distinguishable over the prior art which does not teach or suggest substantially pure compounds or compositions which are non-toxic.

IX. Conclusion

The prior art is silent with respect to providing any particular direction for synthesizing the claimed substantially pure compositions having less than 1% contaminants. By definition, pure materials necessarily differ from less pure or impure materials. See *In Re Kratz and Strasburger*, 201 USPQ 71 (CCPA 1979). Further, the secondary references (Bodansky, Eldefrawi and Hashimoto) that teach alternative synthesis techniques for selectively reacting a polyamine with an acylating agent do not disclose processes that would be expected to yield greater than 99% purity. There can be no doubt that the invention, which is substantially pure and has less than 1% contaminants, is different from the extremely toxic and 99% impure compositions taught by the principal reference (the Cherksey patent), and is also different from any expected product prepared by modifying the teachings of the principal reference in view of the secondary references, which disclose synthesis techniques that yield only about 80% purity or less of different targeted compounds.

It is respectfully submitted that there is not any combination of prior art references which teach or suggest the modifications necessary to achieve the claimed substantially pure compounds having less than 1% contaminants and/or the compositions consisting essentially of compounds in accordance with formula I having a level of contaminants that is non-toxic. The difference between the prior art and the claimed invention is the difference between mere laboratory

curiosities and effective, potentially life-saving therapies. In view of these distinctions, reversal of all prior art rejections and allowance of all claims, including those withdrawn from consideration, is appropriate.

Respectfully submitted,

LARS ERIC SUNDSTROM

By: Price, Heneveld, Cooper, DeWitt & Litton, LLP

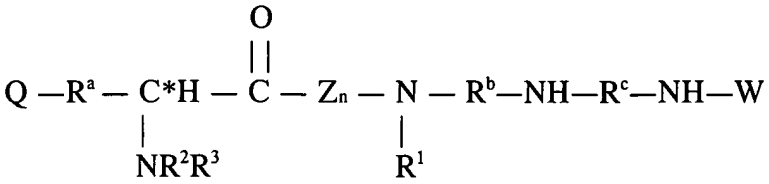
February 27, 2004
Date

Gunther J. Evanina
Registration No. 35 502
695 Kenmoor, S.E.
Post Office Box 2567
Grand Rapids, Michigan 49501
(616) 949-9610

GJE/daw

Appendix of Claims (37 CFR §1.192(c)(9))

1. A substantially pure compound having less than 1% contaminants and having the formula (I)



(I)

wherein:

Q represents an amidino group, a cyano group or a group of formula XYN-, where

X and Y are the same or different, and each may represent a hydrogen atom, a lower alkyl group, or hetero-atom containing group or, together with the nitrogen atom to which they are attached, form a nitrogen-containing heterocyclic group;

R^a represents a straight or branched chain alkylene or alkenylene group having from 1 to 6 carbon atoms and each optionally being substituted by from 1 to 4 alkyl groups each having from 1 to 3 carbon atoms;

R^b and R^c represents an alkylene or alkylene group having 3 or 4 carbon atoms in a straight chain, each being optionally substituted by a 1 or 2 alkyl groups each having from 1 to 3 carbon atoms, the total number of carbon atoms in said straight chains of R^b and R^c being 7;

R^2 and R^3 are the same as or different from each other and each represents a hydrogen atom, or a group of formula R, RCO-, ROCO-, or RNHCO-, where

R represents a lower alkyl group or an aryl group, said alkyl or aryl group being optionally substituted by one or more of the substituents α, defined below;

the chiral carbon atom indicated by the asterisk is in the L configuration;

Z is an aromatic amino acid residue;

n is 0 or 1;

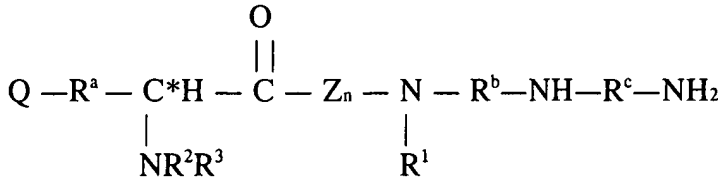
R^1 represents a hydrogen atom or a lower alkyl group or an aryl group, said alkyl or aryl group being optionally substituted by one or more of the substituents α, defined below;

W represents a hydrogen atom or an alkyl or aryl group; and

substituents α are selected from: halogen atoms, amino groups, alkylamino groups, dialkylamino groups, cyano groups, hydroxy groups, alkyl groups (except when the substituted group is akyl), aryl groups, carbamoyl groups, alkylcarbamoyl groups, dialkylcarbamoyl groups and carboxy groups and esters thereof;

and pharmaceutically acceptable salts thereof.

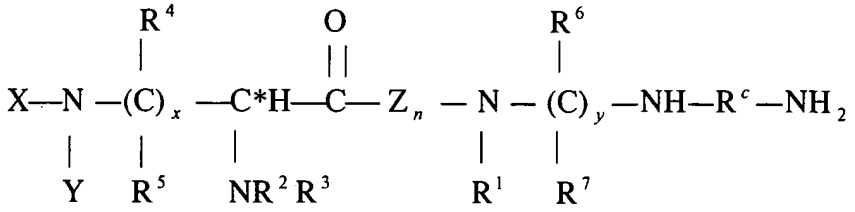
2. A compound according to Claim 1, having the formula (Ia):



(Ia)

wherein Q, R^a, R^b, R^c, R^2, R^3, Z, n, and R^1 are as in Claim 1.

3. Compounds according to Claim 1, having the formula (Ib):



(Ib)

wherein:

X, Y, Z, n and R^1 are as defined in Claim 1;

X is an integer from 1 to 5;

Y is 3 or 4

R^4, R^5, R^6 and R^7 may be the same or different and each represents a hydrogen atom or a lower alkyl group; and

the chiral carbon atom indicated by the asterisk is in the L configuration.

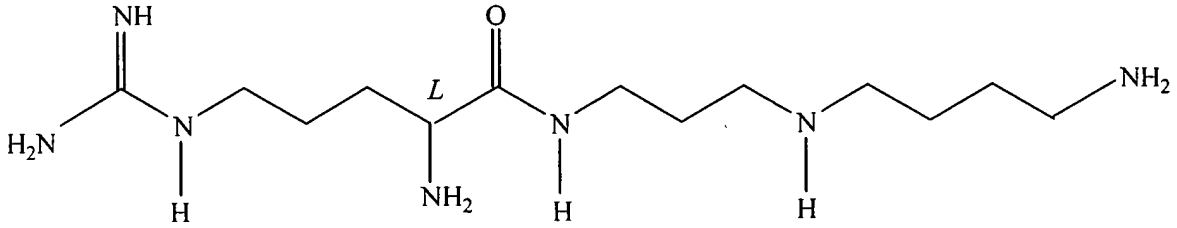
4. Compounds according to Claim 1, in which Z represents an aromatic amino acid residue in the L configuration.

5. A non-toxic compound of formula (I) as defined in Claim 1.

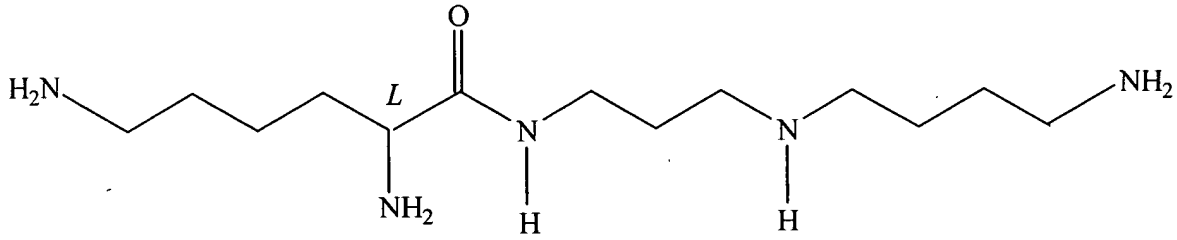
6. A non-toxic compound of formula (Ia) as defined in Claim 2.

7. Non-toxic compounds of formula (Ib) as defined in Claim 3.

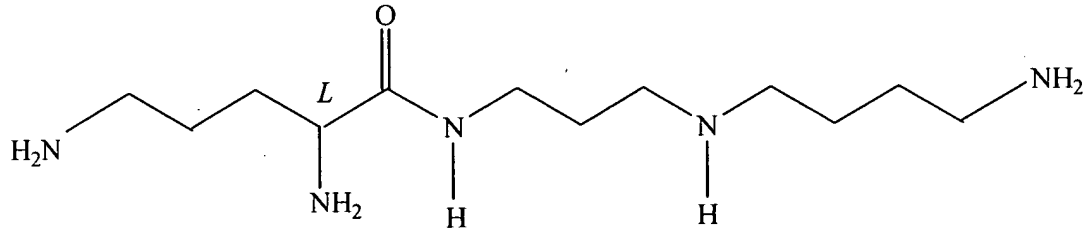
8. A compound according to Claim 1 which is:



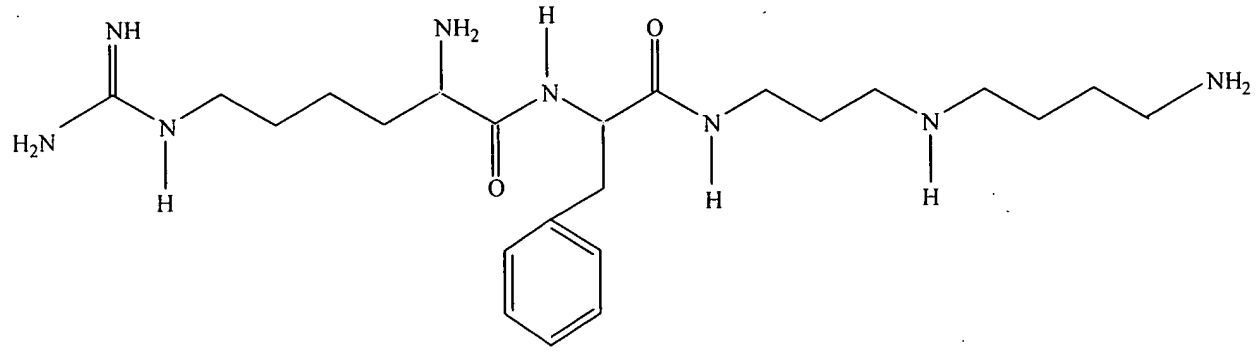
9. A compound according to Claim 1 which is:



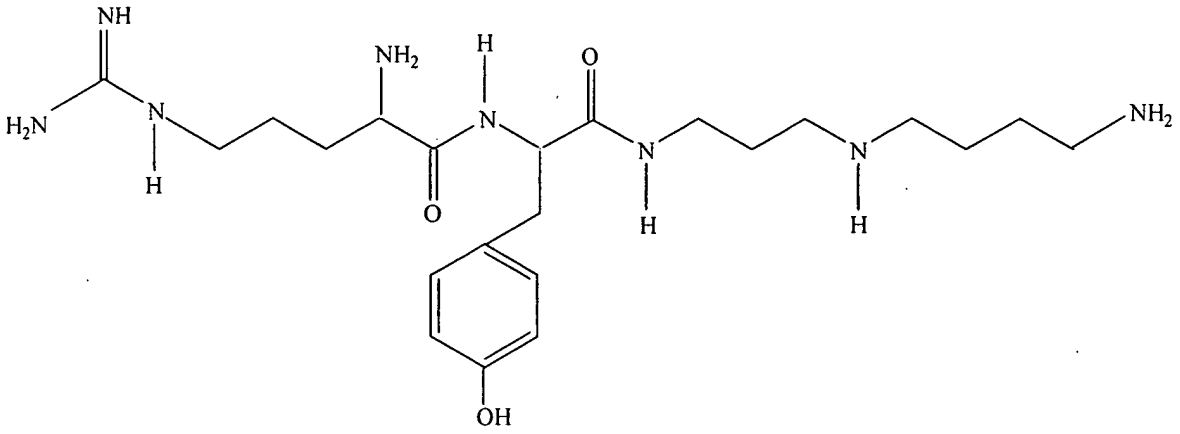
10. A compound according to Claim 1 which is:



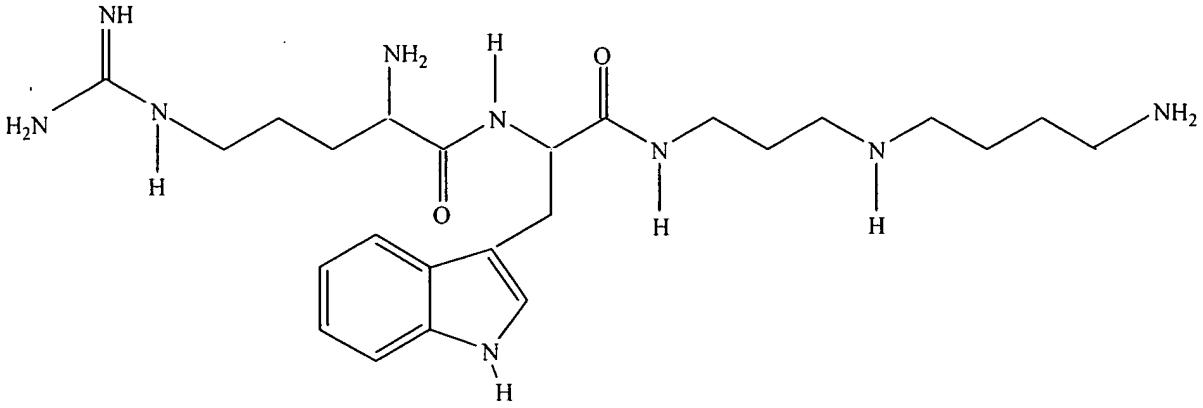
11. A compound according to Claim 1 which is:



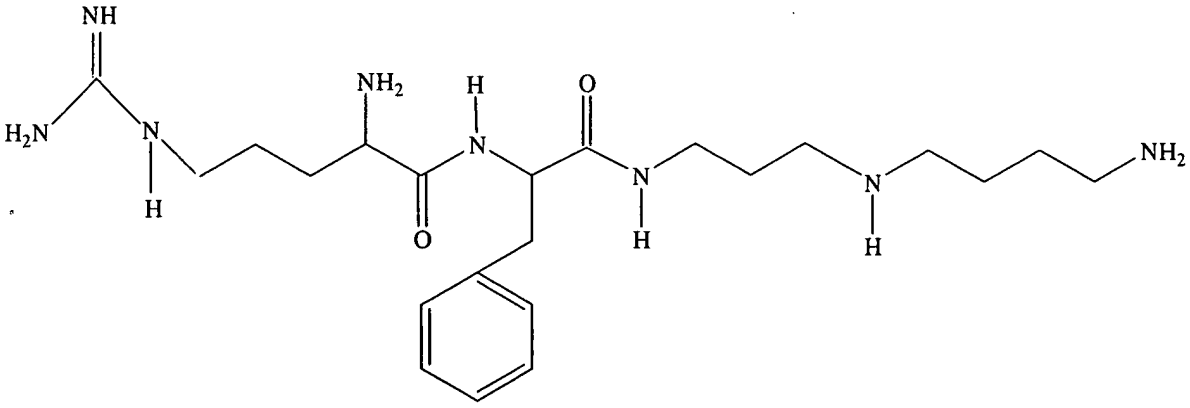
12. A compound according to Claim 1 which is:



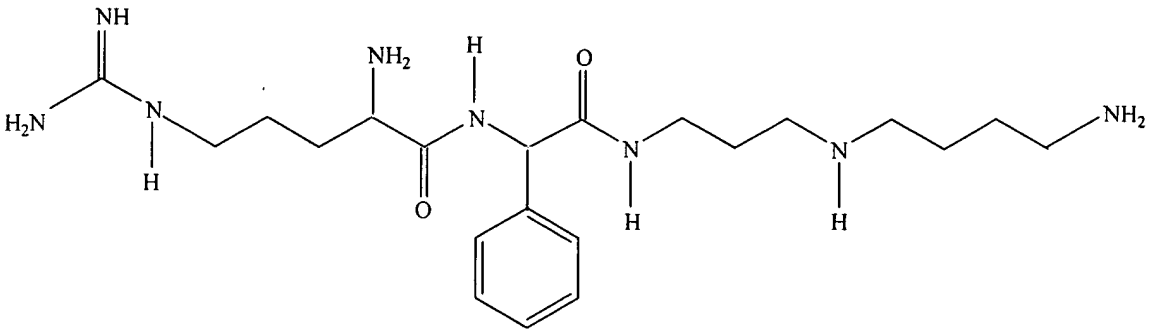
13. A compound according to Claim 1 which is:



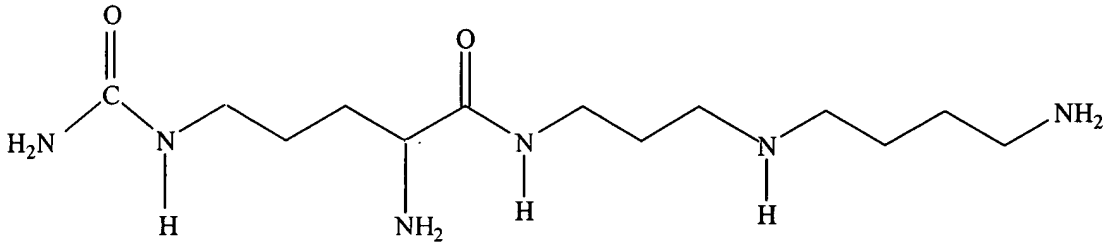
14. A compound according to Claim 1 which is:



15. A compound according to Claim 1 which is:



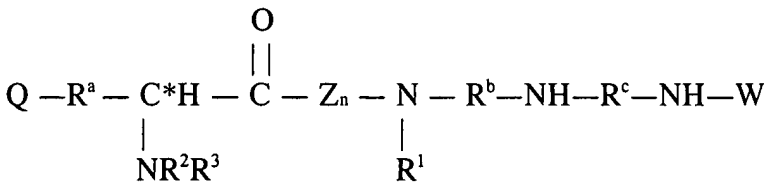
16. A compound according to Claim 1 which is:



17. The use of compound according to Claim 1 for the manufacture of a medicament for treating a mammal to protect said mammal from the neuronal damage caused by an ischaemic event.

18. A method of treating a mammal to protect said mammal from the neuronal damage caused by an ischaemic event by administering to said mammal before, after or during an ischaemic event an effective amount of a non-toxic compound according to Claim 1.

19. A composition consisting essentially of a compound having the formula (I)



(I)

wherein:

Q represents an amidino group, a cyano group or a group of formula XYN-, where

X and Y are the same or different, and each may represent a hydrogen atom, a lower alkyl group, or hetero-atom containing group or, together with the nitrogen atom to which they are attached, form a nitrogen-containing heterocyclic group;

R^a represents a straight or branched chain alkylene or alkenylene group having from 1 to 6 carbon atoms and each optionally being substituted by from 1 to 4 alkyl groups each having from 1 to 3 carbon atoms;

R^b and R^c represents an alkylene or alkylene group having 3 or 4 carbon atoms in a straight chain, each being optionally substituted by a 1 or 2 alkyl groups each having from 1 to 3 carbon atoms, the total number of carbon atoms in said straight chains of R^b and R^c being 7;

R^2 and R^3 are the same as or different from each other and each represents a hydrogen atom, or a group of formula R, RCO-, ROCO-, or RNHCO-, where

R represents a lower alkyl group or an aryl group, said alkyl or aryl group being optionally substituted by one or more of the substituents α, defined below;

the chiral carbon atom indicated by the asterisk is in the L configuration;

Z is an aromatic amino acid residue;

n is 0 or 1;

R^1 represents a hydrogen atom or a lower alkyl group or an aryl group, said alkyl or aryl group being optionally substituted by one or more of the substituents α, defined below;

W represents a hydrogen atom or an alkyl or aryl group; and

substituents α are selected from: halogen atoms, amino groups, alkylamino groups, dialkylamino groups, cyano groups, hydroxy groups, alkyl groups (except when the substituted group is akyl), aryl groups, carbamoyl groups, alkylcarbamoyl groups, dialkylcarbamoyl groups and carboxy groups and esters thereof;

and pharmaceutically acceptable salts thereof;

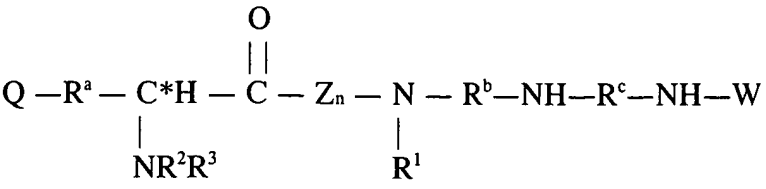
the composition further comprising a level of contaminants that is non-toxic when the composition is administered to a patient in a quantity sufficient to provide a neuroprotective effect.

20. The composition of claim 19, wherein the compound having formula (I) contains less than 1% of contaminants.

21. The composition of claim 19, wherein the composition is non-toxic.

22. The composition of claim 19, wherein the composition does not exhibit unacceptable levels of toxicity at a dosage that is effective for the treatment of hypoxic or ischaemic conditions.

23. A non-toxic composition consisting essentially of a compound having the formula (I)



(I)

wherein:

Q represents an amidino group, a cyano group or a group of formula XYN-, where

X and Y are the same or different, and each may represent a hydrogen atom, a lower alkyl group, or hetero-atom containing group or, together with the nitrogen atom to which they are attached, form a nitrogen-containing heterocyclic group;

R^a represents a straight or branched chain alkylene or alkenylene group having from 1 to 6 carbon atoms and each optionally being substituted by from 1 to 4 alkyl groups each having from 1 to 3 carbon atoms;

R^b and R^c represents an alkylene or alkylene group having 3 or 4 carbon atoms in a straight chain, each being optionally substituted by a 1 or 2 alkyl groups each having from 1 to 3 carbon atoms, the total number of carbon atoms in said straight chains of R^b and R^c being 7;

R^2 and R^3 are the same as or different from each other and each represents a hydrogen atom, or a group of formula R, RCO-, ROCO-, or RNHCO-, where

R represents a lower alkyl group or an aryl group, said alkyl or aryl group being optionally substituted by one or more of the substituents α, defined below;

the chiral carbon atom indicated by the asterisk is in the L configuration;

Z is an aromatic amino acid residue;

n is 0 or 1;

R^1 represents a hydrogen atom or a lower alkyl group or an aryl group, said alkyl or aryl group being optionally substituted by one or more of the substituents α, defined below;

W represents a hydrogen atom or an alkyl or aryl group; and

substituents α are selected from: halogen atoms, amino groups, alkylamino groups, dialkylamino groups, cyano groups, hydroxy groups, alkyl groups (except when the substituted group is akyl), aryl groups, carbamoyl groups, alkylcarbamoyl groups, dialkylcarbamoyl groups and carboxy groups and esters thereof;

and pharmaceutically acceptable salts thereof;

the composition further comprising a level of contaminants that is non-toxic when the composition is administered to a patient in a quantity sufficient to provide a neuroprotective effect.

24. The composition of claim 23 which contains less than 0.1% of contaminants.